COLLEGE OF ONCOLOGY

National Clinical Practice Guidelines

Gastric Cancer

Version 2.2012

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Reference: Lerut T, Stordeur S, Verleye L, Vlayen J, Boterberg T, De Hertogh G, De Mey J, Deprez P, Flamen P, Pattyn P, Van Laethem J-L, Peeters M. Update van de praktijkrichtlijn voor slokdarm- en maagkanker. Good Clinical Practice (GCP). Brussel: Federaal Kenniscentrum voor de Gezonheidszorg (KCE); 2012. KCE reports 179A. D/2012/10.273/32).

or

Reference: Lerut T, Stordeur S, Verleye L, Vlayen J, Boterberg T, De Hertogh G, De Mey J, Deprez P, Flamen P, Pattyn P, Van Laethem J-L, Peeters M. Actualisation des recommandations cliniques pour le cancer de l'oesophage et de l'estomac. Good Clinical Practice (GCP). Bruxelles: Centre Fédéral d'Expertise des Soins de Santé (KCE). 2012. KCE Report 179B. D/2012/10.273/33.

External reviewers and validators

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[1] Attended the open meeting [2] Gave feedback by email

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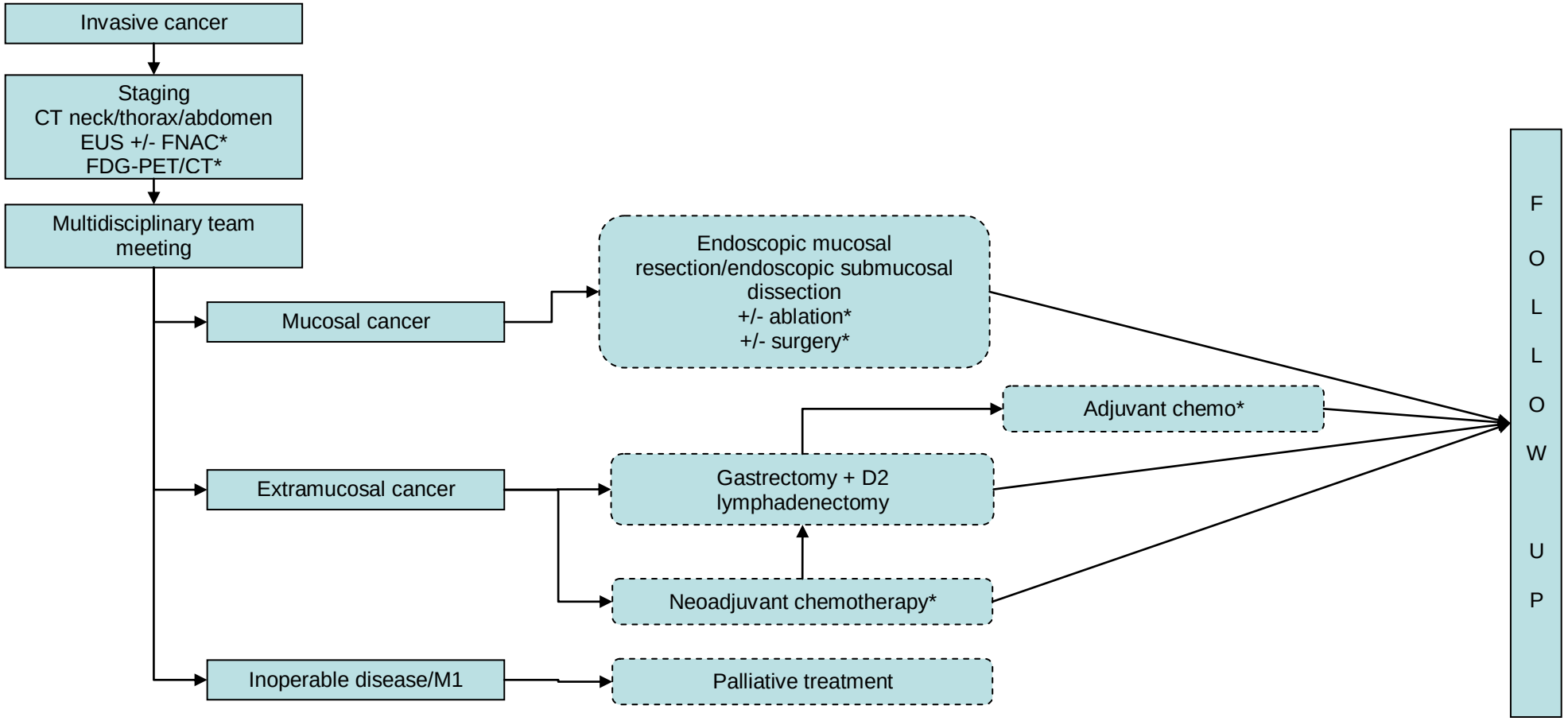
Table of contents

Flowchart: Clinical recommendations for gastric cancer



* Option to be discussed at the MDT meeting

National Guidelines Gastric Cancer

INTRODUCTION [1]

This document presents the updated clinical practice guidelines on gastric cancer which was first published in 2008 [1]. It covers a broad range of topics: staging, treatment and follow-up of patients with confirmed invasive gastric cancer.

Importantly, the following topics that were part of the previous version were not included in the update:

- work-up of pre-invasive lesions, i.e. dysplastic lesions, including high-grade dysplasia
- treatment of gastric lymphoma
- treatment of gastrointestinal stromal tumors (GIST)

For more in-depth information and the scientific background, we would like to ask the readers to consult the full scientific report at www.kce.fgov.be.

The guidelines are developed by a panel of experts (see 'expert panel') comprising clinicians of different specialties and were reviewed by relevant professional associations (see 'external reviewers and validators').

The aim of these guidelines is to assist all care providers involved in the care of patients with gastric cancer.

EPIDEMIOLOGY[2-12]

With an estimated 988 000 new cases in 2008 worldwide (7.8% of all new cancer cases), gastric cancer is in fourth place behind cancers of the lung, breast, and colon and rectum, with more than 70% of the cases occurring in developing countries. It is the second most common cause of death from cancer.

In Belgium, the crude incidence rate of gastric cancer declined from 17.4 per 100.000 males in 2004 to 15.4 per 100 000 males in 2009. In females, the crude incidence rate remained quite stable between 2004 and 2009 (9.4/100 000 females in 2009). Similar trends are reported for the age standardised incidence.

While the incidence rates of gastro-oesophageal junction (GOJ) tumours recently increased, the incidence rates of ‘real’ gastric tumours declined.

SEARCH FOR EVIDENCE [13-16]

Sources

Systematic reviews and meta-analyses were searched in the following databases: OVID Medline and PreMedline, EMBASE, Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects (DARE), Health Technology Assessment (HTA) database. RCTs were searched in OVID Medline, PreMedline, EMBASE and CENTRAL, while diagnostic accuracy studies were searched in OVID Medline, PreMedline and EMBASE.

A date limit was set from August 2007 (i.e. the search date of the previous version) until 2011.

Grade of recommendation

A grade of recommendation was assigned to each recommendation using the GRADE system (Appendix 1).

EXTERNAL REVIEW

The guidelines prepared by the expert panel were circulated to the relevant professional associations (see 'external reviewers'). Each association was asked to assign two key persons to discuss the recommendations during an open meeting. As a preparation of the meeting all invited experts were asked to score each recommendation on a 5-point Likert-scale to indicate their agreement with the recommendation, with a score of '1' indicating 'completely disagree', '2' indicating 'somewhat disagree', '3' indicating 'unsure', '4' indicating 'somewhat agree', and '5' indicating 'completely agree' (the experts were also able to answer 'not applicable' in case they were not familiar with the underlying evidence). In case an expert disagreed with the recommendation (score '1' or '2'), (s)he was asked to provide appropriate evidence. All scores were then anonymized and summarized into a median score, minimum score, maximum score and % of 'agree'-scores (score '4' and '5') to allow a targeted discussion. The recommendations were then discussed during a face-to-face meeting on March 30th 2012. Based on this discussion a final draft of the recommendations was prepared.

As part of the standard KCE procedures, an external scientific validation of the report was conducted by three independent experts. Following this validation procedure, some recommendations were finally adapted if strong arguments supported a change in the formulation.

DEFINITIONS

Topographic definitions [17-20]

- A tumour of which the epicentre is within 5 cm of the GOJ and extending into the oesophagus is to be classified as an oesophageal tumour.
- Tumours with an epicentre in the stomach greater than 5 cm from the GOJ or those within 5 cm of the GOJ without extension in the oesophagus are to be classified as a gastric tumour.

Early lesions [21-50]

- Several classifications are available for dysplasia. For the physician, the used classification should be clinically relevant.

Early versus locally-advanced invasive disease

- Definitions of early and locally-advanced cancer are not uniform and controversial. Therefore, to avoid discussion, an attempt will be made to define the eligible population for our recommendations as accurate as possible.

STAGING [51,52-56,61-70]

Conclusions of the literature update

- For T-staging, CT seems to have a low sensitivity for the diagnosis of T1-2 tumours and a moderate sensitivity for higher T-stages (low level of evidence; Anzidei 2009, Cidon 2009, Hwang 2010, Hye 2009, Kim 2011, Kim 2009, Lee 2009, Lee 2009, Makino 2011, Moschetta 2010, Pan 2010). EUS seems to have a better diagnostic accuracy for the detection of T1 tumours, and has a moderate sensitivity and specificity for the distinction between T1a and T1b tumours (low level of evidence; Mocellin 2011, Kwee 2008).
- For N-staging, CT has a moderate sensitivity and specificity (low level of evidence; Seevaratnam 2011, Kwee 2009). EUS and MRI do not seem to have a better diagnostic accuracy (low level of evidence; Mocellin 2011, Seevaratnam 2011, Kwee 2009). PET and PET/CT have a lower sensitivity but a higher specificity (low level of evidence; Seevaratnam 2011, Kwee 2009). Sentinel lymph node biopsy in patients with T1-2 tumours has a sensitivity similar to that of CT, but a higher specificity (low level of evidence, Wang 2011).
- For the detection of liver metastases, CT and PET(/CT) have a similar low sensitivity and high specificity (low level of evidence, Wang 2011). The diagnostic accuracy of MRI seems to be better (low level of evidence, Wang 2011).
- For the detection of peritoneal metastases, CT, EUS and PET(/CT) have a low sensitivity and a high specificity (low level of evidence, Wang 2011). Laparoscopy seems to have a better diagnostic accuracy (low level of evidence, Leake 2011).

Final recommendations

- All patients diagnosed with gastric cancer should be discussed at a multidisciplinary team meeting ***(strong recommendation, low level of evidence)***.
- In patients with newly diagnosed gastric cancer, CT scan of the chest and abdomen should always be performed ***(strong recommendation, low level of evidence)***.
- Endoscopic ultrasonography (EUS) can be considered in patients planned for curative treatment on the basis of clinical presentation and/or CT ***(weak recommendation, low level of evidence)***. Fine-needle aspiration cytology of suspicious lymph nodes or metastases can be considered if technically feasible.
- The following examinations can be considered for specific indications: PET scan, magnetic resonance imaging, laparoscopy ***(weak recommendation, low level of evidence)***.

Good clinical practice

- Multi-detector, multi-planar reformatted CT scan should be performed with IV contrast and gastric distension with oral contrast or water. The liver should at least be imaged in the arterial and portal venous phase.

TREATMENT OF MUCOSAL CANCER [51,71-79]

Conclusions of the literature update

- Based on observational studies, excellent cure rates and survival can be achieved with endoscopic treatment of early gastric cancer (T1) if

standard indications are applied (low level of evidence; Bennett 2009).

- Based on observational studies, endoscopic submucosal dissection seems to be associated with a higher curative resection rate, a lower local recurrence rate, but a higher perforation rate than endoscopic mucosal resection. Both interventions are equally effective in terms of survival (low level of evidence; Park 2011).
- Insufficient evidence is available to draw conclusions on the effectiveness of photodynamic therapy, laser or argon plasma coagulation for the treatment of early gastric cancer.

Final recommendations

- Endoscopic mucosal resection (EMR) or endoscopic submucosal dissection (ESD) should be performed whenever possible for a T1a gastric cancer aiming at staging and curative resection. If the staging and R0 resection is pathologically confirmed, the procedure can be considered therapeutic, taking into account other well-defined criteria relating to size, histological type, lymphovascular invasion and differentiation grade ***(weak recommendation, low level of evidence)***.
- (Destructive) mucosal ablative techniques cannot be recommended as a curative option for patients with T1a gastric cancer and should be limited to centres with appropriate expertise ***(weak recommendation, very low level of evidence)***.

Good clinical practice

- Resection specimens of EMR and ESD should be reviewed by an experienced pathologist in this area and discussed at a multidisciplinary meeting with access to the clinical information.

TREATMENT OF CANCER BEYOND THE MUCOSA

Neoadjuvant treatment [57,80-87]

Conclusions of the literature update

- Neoadjuvant chemotherapy is associated with a survival benefit compared with surgery alone in patients with locally advanced gastric cancer eligible for potentially curative surgery (moderate level of evidence; Li 2010). The benefit seems to be larger in T3-4 tumours (low level of evidence; Li 2010).
- Perioperative chemotherapy seems to be associated with a survival benefit in patients with gastric cancer (low level of evidence; Cunningham 2006).
- Preoperative radiotherapy seems to improve local control and 5-year survival in patients with resectable gastric cancer compared to no adjuvant therapy (low level of evidence; Valentini 2009).

Final recommendations

- If after multidisciplinary discussion neoadjuvant treatment is considered for a locally-advanced gastric tumour, neoadjuvant chemotherapy is recommended ***(strong recommendation, moderate level of evidence)***.

Surgical treatment [51,58,88-98]

Conclusions of the literature update

- Randomized studies to support the use of surgery as standard treatment for patients with resectable gastric cancer is lacking.
- In patients with resectable gastric cancer, D2 lymphadenectomy is associated with similar overall survival and recurrence rates as D1 lymphadenectomy (high level of evidence; Memon 2011), but with a significantly increased morbidity (low level of evidence; Memon 2011). This morbidity seems to be related to the splenectomy and/or pancreatectomy performed as part of the D2 lymphadenectomy (low level of evidence; Roberts 2011).
- In patients with resectable gastric cancer, para-aortic lymph node dissection is not associated with a survival benefit (moderate level of evidence; Zheng 2011, Lustosa 2008).
- Pouch reconstruction seems to be associated with better food intake and improved quality of life (high level of evidence; Gertler 2009).
- In patients with resectable gastric cancer, laparoscopic gastrectomy is associated with fewer postoperative complications compared with open gastrectomy, but a longer operation time and a reduced number of lymph nodes harvested (low level of evidence; Zorcolo 2011, Chen 2009).
- Postoperative mortality after gastrectomy for gastric cancer seems to be associated with the surgeon and hospital volume (low level of evidence; Halm 2002, Killeen 2005).

Final recommendations

- Surgical resection should be considered standard treatment for patients with resectable gastric cancer ***(strong recommendation, low level of evidence)***.
- Surgery for gastric cancer should aim at achieving an R0 resection ***(strong recommendation, low level of evidence)***.
- D2 lymphadenectomy should be standard during gastrectomy and performed in high-volume, specialized centres with experience and/or specialist training ***(weak recommendation, low level of evidence)***.
- Splenectomy and pancreatectomy should not be considered standard practice during gastrectomy if no disease infiltration in the spleen or pancreas is present ***(weak recommendation, low level of evidence)***.
- Laparoscopic surgery should be restricted to clinical studies ***(weak recommendation, low level of evidence)***.

Adjuvant treatment [51,57,59,82,85-86,99-118]

Conclusions of the literature update

- Postoperative adjuvant chemotherapy significantly improves overall survival in patients with resectable gastric cancer compared to no adjuvant therapy (moderate level of evidence; GASTRIC 2010, Sun 2009, Liu 2008).
- There are indications that perioperative chemotherapy improves the overall survival of patients with gastric cancer (low level of evidence; Cunningham 2006).
- Adjuvant oral fluorinated pyrimidines are associated with a survival benefit compared to surgery alone (high level of evidence; Sun 2009).

- Postoperative radiotherapy is not associated with a survival benefit in patients with gastric cancer (low level of evidence; Valentine 2009).
- No definite conclusions can be drawn on the effectiveness of postoperative chemoradiation (low level of evidence; CCO 2003).
- Postoperative hyperthermic intraperitoneal chemotherapy can improve overall survival in patients with resectable gastric cancer compared to no adjuvant therapy (moderate level of evidence; Yan 2007).
- The benefits of immunochemotherapy are currently unclear (low level of evidence; CCO 2003).

Final recommendations

- Patients with gastric cancer who received neoadjuvant chemotherapy can be considered for postoperative chemotherapy ***(weak recommendation; low level of evidence)***.
- Postoperative chemotherapy and chemoradiotherapy can be considered for patients with gastric cancer who did not receive neoadjuvant chemotherapy ***(weak recommendation; low level of evidence)***.
- Postoperative radiotherapy alone is not recommended for patients with gastric cancer ***(weak recommendation; low level of evidence)***.

TREATMENT OF METASTATIC DISEASE [51,60-61,119-139]

Conclusions of the literature update

- Palliative gastrectomy seems to be associated with a lower mortality than gastric bypass for patients with unresectable gastric cancer (low level of evidence; SIGN 2006).
- Laparoscopic gastrojejunostomy seems to be associated with a shorter time to oral intake and a shorter hospital stay than open gastric bypass for patients with unresectable gastric cancer (low level of evidence; Mahar 2011).
- There is weak evidence that adding HIPEC to cytoreductive surgery in patients with peritoneal metastases is associated with a survival benefit (low level of evidence; Yang 2011).
- In patients with malignant gastric outlet obstruction, endoscopic stenting and surgical gastroenterostomy have similar survival rates (low level of evidence; Zheng 2011, Ly 2010). Inconsistent evidence is available on the associated risks.
- In patients with advanced or metastatic gastric cancer, combination chemotherapy has a survival benefit compared to single agent chemotherapy (high level of evidence; Wagner 2010).
- Oral 5-FU analogues seem to be associated with a survival benefit compared with intravenous 5-FU (moderate level of evidence; Huang 2010, Ma 2011).
- In HER2-positive gastric cancer, adding trastuzumab to standard chemotherapy seems to be associated with a survival benefit (low level of evidence; Bang 2010).

Final recommendations

- Palliative gastric surgery is limited to symptomatic stenoses, bleeding tumours and perforation ***(weak recommendation, low level of evidence)***.

- For patients with malignant gastric outlet obstruction, treatment options include endoscopic stenting or surgical gastroenterostomy ***(weak recommendation, low level of evidence)***.
- In patients with locally advanced or metastatic cancer of the stomach with good performance status combination chemotherapy is recommended ***(strong recommendation, high level of evidence)***.
- Patients with advanced gastric cancer should have access to a specialist palliative care team, in particular in relation to comfort and symptom control, nutrition and quality of life ***(strong recommendation, low level of evidence)***.

FOLLOW-UP [51,75,139-140]

Conclusions of the literature update

- In routine follow-up, CT seems to have a low sensitivity and moderate specificity to detect recurrence after curative gastrectomy for gastric cancer (low level of evidence; Kim 2009). The diagnostic accuracy of PET/CT is not clearly better (low level of evidence; Kim 2009, Graziosi 2011, Sim 2009).
- Conflicting evidence is available on the diagnostic accuracy of PET/CT in patients with a suspected recurrence of gastric cancer (low level of evidence; Bilici 2011, Park 2009).

Final recommendations

- It is recommended that the follow-up of patients treated for gastric cancer includes a physical examination and blood analysis every three months, with targeted imaging if needed. A CT scan can be considered every six months in the first year and then annually until the fifth year ***(weak recommendation; very low level of evidence)***.
- Patients treated with endoscopic mucosal resection (EMR) or endoscopic submucosal dissection (ESD) should have a follow-up endoscopy after three months, then every six months in the first two years, and then annually ***(weak recommendation; very low level of evidence)***.

Treatment of recurrent disease [141-147]

Conclusions of the literature update

- No good evidence is available about the optimal treatment for patients with recurrent gastric cancer.

Final recommendations

- In patients with recurrent gastric cancer, treatment options should be discussed in the multidisciplinary team (strong recommendation; very low level of evidence).

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Appendix 1: GRADE system

Levels of evidence according to the GRADE system

Quality level	Definition	Methodological Quality of Supporting Evidence
High	We are very confident that the true effect lies close to that of the estimate of the effect	RCTs without important limitations or overwhelming evidence from observational studies
Moderate	We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different	RCTs with important limitations (inconsistent results, methodological flaws, indirect, or imprecise) or exceptionally strong evidence from observational studies
Low	Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect	RCTs with very important limitations or observational studies or case series
Very low	We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of the effect	

Strength of recommendations according to the GRADE system

Grade	Definition
Strong	The desirable effects of an intervention clearly outweigh the undesirable effects *(the intervention is to be put into practice)*, or the undesirable effects of an intervention clearly outweigh the desirable effects *(the intervention is not to be put into practice)*
Weak	The desirable effects of an intervention probably outweigh the undesirable effects *(the intervention probably is to be put into practice)*, or the undesirable effects of an intervention probably outweigh the desirable effects *(the intervention probably is not to be put into practice)*

Appendix 2: TNM classification and stage grouping (7th edition)

cTNM Clinical Classification

T – Primary tumour

Tx Primary tumor cannot be assessed
T0 No evidence of primary tumor
Tis Carcinoma in situ: intraepithelial tumour without invasion of the lamina propria, high grade dysplasia
T1 Tumour invades lamina propria, muscularis mucosae, or submucosa
- T1a Tumour invades lamina propria or muscularis mucosae
- T1b Tumour invades submucosa

T2 Tumour invades muscularis propria
T3 Tumour invades subserosa
T4 Tumour perforates serosa or invades adjacent structures[1,2,3]
- T4a Tumour perforates serosa
- T4b Tumour invades adjacent structures[1,2,3]

Note:
1. The adjacent structures of the stomach are the spleen, transverse colon, liver, diaphragm, pancreas, abdominal wall, adrenal gland, kidney, small intestine, and retroperitoneum.
2. Intramural extension to the duodenum or oesophagus is classified by the depth of greatest invasion in any of these sites, including stomach.
3. Tumour that extends into gastrocolic or gastrohepatic ligaments or into greater of lesser omentum, without perforation of visceral peritoneum, is T3.

N – regional lymph nodes

Nx Regional lymph nodes cannot be assessed
N0 No regional lymph node metastasis
N1 Metastasis in 1 to 2 regional lymph nodes
N2 Metastasis in 3 to 6 regional lymph nodes
N3 Metastasis in 7 or more regional lymph nodes
- N3a Metastasis in 7-15 regional lymph nodes
- N2b Metastasis in 16 or more regional lymph nodes

M – Distant metastasis

M0	No distant metastasis
M1	Distant metastasis

Note: Distant metastasis includes peritoneal seeding, positive peritoneal cytology, and omental tumour not part of continuous extension.

pTNM Pathological Classification

The pT and pN categories correspond to the T and N categories.

pN0 Histological examination of a regional lymphadenectomy specimen will ordinarily include 16 or more lymph nodes.
If the lymph nodes are negative, but the number ordinarily examined is not met, classify as pN0.

pM – Distant Metastasis

pM1 Distant metastasis microscopically confirmed

Note: pM0 and pMx are not valid categories

Stage grouping

Stage 0	Tis	N0	M0
Stage IA	T1	N0	M0
Stage IB	T2	N0	M0
	T1	N1	M0
Stage IIA	T3	N0	M0
	T2	N1	M0
	T1	N2	M0
Stage IIB	T4a	N0	M0
	T3	N1	M0
	T2	N2	M0
	T1	N3	M0
Stage IIIA	T4a	N1	M0
	T3	N2	M0
	T2	N3	M0
Stage IIIB	T4b	N0, N1	M0
	T4a	N2	M0
	T3	N3	M0
Stage IIIC	T4a	N3	M0
	T4b	N2, N3	M0
Stage IV	Any T	Any N	M1